

PATENT COOPERATION TREATY

1FD

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

WOLF, GREENFIELD & SACKS, P.C.
Attn: Chen, Tani
600 Atlantic Avenue
Federal Reserve Plaza
Boston, Massachusetts 02210
ETATS-UNIS D'AMERIQUE

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing
(day/month/year)

19/05/2010

Applicant's or agent's file reference

S1509.70040

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No.

PCT/US2009/003750

International filing date
(day/month/year)

24/06/2009

Applicant

STRATEGIC SCIENCE & TECHNOLOGIES, LLC

1. ☒ The applicant is hereby notified that the International search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 338.82.70

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

Shortly after the expiration of 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within 19 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise, the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office Practice and the PCT Applicant's Guide, National Chapters.

RECEIVED

Wolf, Greenfield & Sacks, P.C.

Name and mailing address of the International Searching Authority

European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel: (+31-70) 340-2040
Fax: (+31-70) 340-3016

Authorized officer

Jette Christensen
Not Required
Initials 1st 2nd

MAY 25 2010

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Annex B).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the international Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, International Phase, paragraph 296).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the International phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/s filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet or sheets containing a complete set of claims in replacement of all the claims previously filed must be submitted.

Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively in Arabic numerals (Section 205(a)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must, preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/PEA/401).

If a demand for international preliminary examination is made, the written opinion of the International Searching Authority will, except in certain cases where the International Preliminary Examining Authority did not act as International Searching Authority and where it has notified the International Bureau under Rule 66.1(b)(b), be considered to be a written opinion of the International Preliminary Examining Authority. If a demand is made, the applicant may submit to the International Preliminary Examining Authority a reply to the written opinion together, where appropriate, with amendments before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later (Rule 43bis.1(c)).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see the *PCT Applicant's Guide*, National Chapters.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference S1509_70040	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US2009/003750	International filing date (day/month/year) 24/06/2009	(Earliest) Priority Date (day/month/year)
Applicant STRATEGIC SCIENCE & TECHNOLOGIES, LLC		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 6 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of:

☒ the international application in the language in which it was filed
☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

- b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6bis(a)).
 c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (See Box No. II)

3. ☐ **Unity of invention is lacking** (see Box No. III)

4. With regard to the **title**,

☐ the text is approved as submitted by the applicant
☒ the text has been established by this Authority to read as follows:

TOPICAL COMPOSITION CONTAINING NAPROXEN

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant
☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings**,

- a. the figure of the **drawings** to be published with the abstract is Figure No. _____
☐ as suggested by the applicant
☐ as selected by this Authority, because the applicant failed to suggest a figure
☐ as selected by this Authority, because this figure better characterizes the invention
 b. ☐ none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/003750

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/19 A61K9/06
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006/096360 A1 (ISW GROUP INC [US]; SPANN-WADE MONIQUE [US]; WARD ANTHONY J [US]) 14 September 2006 (2006-09-14) the whole document paragraphs [0055], [0239]; table 1a paragraphs [0020], [0030], [0173], [0189] - [0195], [0227], [0245]	111
X	US 2007/253911 A1 (TAMARKIN DOV [IL] ET AL) 1 November 2007 (2007-11-01)	111
Y	the whole document paragraph [0414]	1-112
	----- -/-	

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
 "E" earlier document but published on or after the international filing date
 "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
 "O" document referring to an oral disclosure, use, exhibition or other means
 "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
 "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
 "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
 "Z" document member of the same patent family

Date of the actual completion of the international search

10 May 2010

Date of mailing of the international search report

19/05/2010

Name and mailing address of the ISA/

European Patent Office, P.B. 5618 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Luangkhot, Nathalie

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/003750

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99/13717 A1 (STRATEGIC SCIENCE & TECHNOLOGI [US]) 25 March 1999 (1999-03-25)	1-112
Y	the whole document claims 83,84 page 2, line 23 page 8, last paragraph - page 9, paragraph 2 claims 1,6,7,8,70,75 table 3	1-112
X	WO 2005/102282 A1 (STRATEGIC SCIENCE & TECHNOLOGI [US]; FOSSEL ERIC THOR [US]) 3 November 2005 (2005-11-03)	1-112
Y	the whole document page 18, lines 12-22,23-30 page 17, line 25 - page 18, line 11 examples 1-3 claims 64,65,66,71,73,,83,86 claims 1,13,14,30,32,57-63 table 3	1-112
X	WO 2005/102307 A2 (STRATEGIC SCIENCE & TECHNOLOGI [US]; FOSSEL ERIC THOR [US]) 3 November 2005 (2005-11-03)	1-112
Y	the whole document page 18, lines 13-23,24-29; table 3 page 17, line 18 - page 18, line 12 examples 4-6 claims 1,4,5,8,10,18,23	1-112

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2009/003750

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claim: 111

A composition for topical delivery to the skin of a subject, the composition comprising:

- a/ naproxen and/or an naproxen salt;
- b/ a stabilization polymer;
- c/ propylene glycol;
- d/ a polysorbate surfactant.

2. claim: 112

A composition for topical delivery to the skin of a subject, the composition comprising:

- the same ingredients a/, b/, c/ and d/ as in claim 111, and further comprising:
- e1/ at least one chloride salt and
- g/ water.

3. claims: 1-110

A composition for topical delivery to the skin of a subject, the composition comprising:

- the same ingredients a/, b/, c/ and d/ as in claim 111, and further comprising:
- e2/ a hostile biophysical environment,
- f/ a nitric oxide donor.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2009/003750

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 2006096360	A1	14-09-2006	AU 2006220964 A1	14-09-2006
			BR P10608077 A2	10-11-2009
			CA 2599968 A1	14-09-2006
			EP 1858503 A1	28-11-2007
			JP 2008531693 T	14-08-2008
			KR 20080008321 A	23-01-2008
			US 2007053984 A1	08-03-2007
US 2007253911	A1	01-11-2007	NONE	
WO 9913717	A1	25-03-1999	AT 456302 T	15-02-2010
			AU 737199 B2	09-08-2001
			AU 9318698 A	05-04-1999
			CA 2303394 A1	25-03-1999
			EP 2158907 A2	03-03-2010
			EP 1041880 A1	11-10-2000
			JP 4352114 B2	28-10-2009
			JP 2002515401 T	28-05-2002
			JP 2009143968 A	02-07-2009
WO 2005102282	A1	03-11-2005	AU 2005235308 A1	03-11-2005
			AU 2005235309 A1	03-11-2005
			CA 2563670 A1	03-11-2005
			CA 2563678 A1	03-11-2005
			EP 1737441 A2	03-01-2007
			EP 1737429 A1	03-01-2007
			JP 2007532696 T	15-11-2007
			JP 2007532697 T	15-11-2007
			US 2009123528 A1	14-05-2009
			US 2009221536 A1	03-09-2009
			US 2008280984 A1	13-11-2008
			WO 2005102307 A2	03-11-2005
WO 2005102307	A2	03-11-2005	AU 2005235308 A1	03-11-2005
			AU 2005235309 A1	03-11-2005
			CA 2563670 A1	03-11-2005
			CA 2563678 A1	03-11-2005
			EP 1737441 A2	03-01-2007
			EP 1737429 A1	03-01-2007
			JP 2007532696 T	15-11-2007
			JP 2007532697 T	15-11-2007
			US 2009123528 A1	14-05-2009
			US 2009221536 A1	03-09-2009
			US 2008280984 A1	13-11-2008
			WO 2005102282 A1	03-11-2005

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2009/003750

International filing date (day/month/year)
24.06.2009

Priority date (day/month/year)

International Patent Classification (IPC) or both national classification and IPC
INV. A61K31/19 A61K9/06

Applicant
STRATEGIC SCIENCE & TECHNOLOGIES, LLC

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office

D-80298 Munich
Tel. +49 89 2399 - 0
Fax: +49 89 2399 - 4465

Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

Luangkhot, Nathalie

Telephone No. +49 89 2399-7857



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2009/003750

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the International application, this opinion has been established on the basis of a sequence listing filed or furnished:
 - a. (means)
 - ☐ on paper
 - ☐ in electronic form
 - b. (time)
 - ☐ in the international application as filed
 - ☐ together with the international application in electronic form
 - ☐ subsequently to this Authority for the purposes of search
4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2009/003750

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 55, 84, 109, 110

because:

☒ the said international application, or the said claims Nos. 55, 84, 109, 110 relate to the following subject matter which does not require an international search (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

☐ no international search report has been established for the whole application or for said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13ter.1(a) or (b).

☐ See Supplemental Box for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2009/003750

Box No. IV Lack of unity of invention

1. ☐ In response to the invitation (Form PCT/ISA206) to pay additional fees, the applicant has, within the applicable time limit:
- ☐ paid additional fees
 - ☐ paid additional fees under protest and, where applicable, the protest fee
 - ☐ paid additional fees under protest but the applicable protest fee was not paid
 - ☐ not paid additional fees
2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☒ all parts.
 - ☐ the parts relating to claims Nos. 1-112

Box No. V Reasoned statement under Rule 43b/s.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>1-110, 112</u>
	No: Claims	<u>111</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-112</u>
Industrial applicability (IA)	Yes: Claims	<u>1-54, 56-83, 85-108, 111, 112</u>
	No: Claims	

2. Citations and explanations

see separate sheet

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2009/003750

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item I

Basis of the report

The documents cited in the International Search Report (ISR) were numbered respectively from D1-D5; this numbering results from the citation order in the ISR and will be used for the procedure. Unless otherwise specified, the cited passages of each document in the ISR will be considered.

- D1 WO 2006/096360 A1 (ISW GROUP INC [US]; SPANN-WADE MONIQUE [US]; WARD ANTHONY J [US]) 14 September 2006 (2006-09-14)
- D2 US 2007/253911 A1 (TAMARKIN DOV [IL] ET AL) 1 November 2007 (2007-11-01)
- D3 WO 99/13717 A1 (STRATEGIC SCIENCE & TECHNOLOGI [US]) 25 March 1999 (1999-03-25)
- D4 WO 2005/102282 A1 (STRATEGIC SCIENCE & TECHNOLOGI [US]; FOSSEL ERIC THOR [US]) 3 November 2005 (2005-11-03)
- D5 WO 2005/102307 A2 (STRATEGIC SCIENCE & TECHNOLOGI [US]; FOSSEL ERIC THOR [US]) 3 November 2005 (2005-11-03)

Re Item III

1) Claims 55,84,109,110 are directed to a method of treatment. They relate to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv) / 67.1(iv) PCT.

Re Item IV

Lack of unity of invention

2) Non-Unity objection (Rule 13.1 PCT)

2a) The separate inventions/groups of inventions are:

First group of inventions: claim 111 (with the broadest scope)

A composition for topical delivery to the skin of a subject, the composition comprising:

- a/ naproxen and/or a naproxen salt;

- b/ a stabilization polymer;
- c/ propylene glycol;
- d/ a polysorbate surfactant.

Second group of inventions: claim 112

A composition for topical delivery to the skin of a subject, the composition comprising:

- the same ingredients a/, b/, c/ and d/ as in claim 111, and further comprising:
- e1/ at least one chloride salt and
- g/ water.

Third group of inventions: claims: 1-110

A composition for topical delivery to the skin of a subject, the composition comprising:

- the same ingredients a/, b/, c/ and d/ as in claim 111, and further comprising:
- e2/ a hostile biophysical environment,
- f/ a nitric oxide donor.

b2b) The problem to be solved in present application can be seen in the provision of a topical composition containing ibuprofen.

The common concept between the 3 inventions is topical composition containing:

- a/ naproxen and/or a naproxen salt;
- b/ a stabilization polymer;
- c/ propylene glycol;
- d/ a polysorbate surfactant.

However such composition has already been described in D2 (see [0414].

It follows that the common concept between the 3 inventions is not novel in view of D2 and not inventive in view of D1 (see Table 1a in paragraph [00239]; the skilled person willing to find an alternative to ibuprofen would use naproxen; further [0055] clearly says that a thickening agent is an agent that imparts stability).

As the present application provides 3 distinguishable technical solutions, i.e. 3 distinguishable compositions as mentioned above (inventions 1-3), no unifying concept can be acknowledged between the 3 inventions.

2c) It should be noted that the terms "hostile biophysical environment" lacks clarity (Art. 6 PCT) and is interpreted in a broad sense (i.e. any compound that has an effect on the biophysical environment; this can include any compounds and in particular penetrating agents- see for example D4 p.17-27, p.9 L.23-25, claim 16). The same remark applies to the terms "stabilization polymer" which is obscure and extremely broad.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

3) Novelty and inventive step (Art.33(2) and 33(3) PCT)

3a) First invention: claim 111

The subject-matter of independent claim 111 is not novel in the light of D2 (see [0414]) because this latter describes a topical composition containing naproxen, propylene glycol, a polysorbate surfactant and xanthan gum and methyl cellulose functioning as a stabilization polymer.

The subject-matter of claim 111 does not involve an inventive step in view of D1 (see Table 1a in paragraph [00239]: the skilled person willing to find an alternative to ibuprofen would use naproxen instead; further [0055] clearly says that a thickening agent is an agent that imparts stability).

3b) Second invention claim 112

The subject-matter of independent claim 112 is formally novel because none of the cited documents describes explicitly a composition containing a/, b/, c/ d/ and e1/ (a chloride salt).

However it does not involve an inventive in view D4 (or D3: see claim 85 or D5: see p. 18 L.13-20) taken alone:

D4 describes on p.18 L.12-22 a cream containing b/ a collagen which can be seen as a stabilization polymer, c/ propylene glycol, d/ a polysorbate surfactant, e1/ chloride salts such as sodium chloride, magnesium chloride and/or choline chloride. The cream of D4 shows a good penetration (see p.9 L.23-25), an increase in local blood flow (p.12 L.5-7, p.13 L.10-12, p.17 L.22-27, Examples 1-3)...

The only difference is that the said cream does not include in an explicit manner a beneficial substance, e.g. naproxen.

The problem to be solved may be seen in the provision of a naproxen cream having good penetration and an increase in local blood flow.

The solution is the use of the cream of p.18 L.12-20 as base and combine it with the beneficial substance naproxen, which has been explicitly cited in D4.

The skilled man in the art, reading the teachings in D4, does not need to be inventive by adding naproxen to the cream, and arrive at the claimed subject-matter. Thus an inventive cannot be acknowledged.

3c) Third invention claim 1-110

Novelty:

The subject-matter of independent claim 1, and its dependent claims, is formally novel because none of the cited documents describes explicitly a composition containing a/, b/, c/, d/, e2/ (a hostile biophysical environment) and f/.

The subject-matter of independent claim 56, and its dependent claims, is formally novel because none of the cited documents describes explicitly a composition containing a/, b/, c/, d/, e1/ (a chloride salt) and f/.

The subject-matter of independent claims 85 or 104, and its dependent claims, is formally novel because none of the cited documents describes explicitly a composition containing a/, b/, c/, d/, e1/ , f/, g/ and other ingredients such as glyceryl stearate, cetyl alcohol, squalane, Isopropyl myristate, and oleic acid.

The subject-matter of independent claim 110 is formally novel because none of the cited documents describes explicitly a method comprising the application of a composition as described in claim 1.

Inventive step:

However the subject-matter of claims 1 or 56 does not involve an inventive in view D4 (or D3: see claim 85 or D5: see p.18 L.13-20) taken alone:

D4 describes on p.18 L.12-22 a cream containing b/ a collagen which can be seen as a stabilization polymer, c/ propylene glycol, d/ a polysorbate surfactant, e1/ chloride salts such as sodium chloride, magnesium chloride and/or choline chloride functioning as e2/ a hostile biophysical environment, f/ L-arginine functioning as a nitric oxide donor, g/ water, and other ingredients such as glyceryl stearate, cetyl alcohol and squalane. The cream of D4 shows a good penetration (see p.9 L.23-25), an increase in local blood flow (p.12 L.5-7, p.13 L.10-12, p.17 L.22-27, Examples 1-3)...

The only difference is that the said cream does not include in an explicit manner a beneficial substance, e.g. naproxen.

The problem to be solved may be seen in the provision of a naproxen cream having good penetration and an increase in local blood flow.

The solution is the use of the cream of p.18 L.12-20 as base and combine it with the beneficial substance naproxen, which has been explicitly cited in D4.

The skilled man in the art, reading the teachings in D4, does not need to be inventive by adding naproxen to the cream, and arrive at the claimed subject-matter. Thus an inventive cannot be acknowledged.

Dependent claims do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step (see in particular D2: §414 for xanthan gum, isopropyl myristate, glyceryl monostearate, stearyl alcohol; D3: Table 3; D4 or D5: Table 3, p.18 L.23-26 for isopropyl myristate, oleic acid, etc..).

In particular as long as the applicant has not shown with support of comparative test a surprising effect attributed to the use of the specific xanthan gum (present claims 32-38, 76, 96, 97, 105, 106), isopropyl myristate and/or oleic acid (present claims 85 or 104), an inventive step cannot be acknowledged.

3d) Should the applicant renders the subject-matter of the present application novel by pointing out the importance a technical feature that is not described explicitly in prior art or by introducing into the claims the use of a **specific ingredient or a specific amount** or whatever, inventive step may be recognized **only if he demonstrates that a surprising and/or synergistic effect** (with support of experimental data comparing the properties of present and prior art compositions) is attributed to the distinguishing technical feature that the skilled man in the art will not be able to deduct from the prior art.

In the absence of a **surprising effect** directly attributed to the distinguishing feature or **evidence of a particular prejudice**, inventive step cannot be acknowledged because the introduced/distinguishing technical feature will be considered as an **obvious alternative** that the skilled man in the art will perform **routinely**.

The applicant is respectfully requested to identify the closest prior art document(s) and to apply the problem-solution approach.

Re Item VII

Certain defects in the international application

4) Contrary to the requirements of Rule 5.1(a)(ii) PCT, it seems that the relevant background art disclosed in the documents D1-D2 and D4 is not mentioned in the description, nor are these documents identified therein.

5) The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment. Patentability, in particular novelty and inventive step, of claim(s) 55,84,109,110 has been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the compound/composition.

Re Item VIII

Certain observations on the international application

5) Severe clarity objections (Art.6 PCT)

5a) Too many independent claims

The present application contains too many independent claims (see claims 1,56,85, 104,110,111 and 112). They appear to relate to a product claim (i.e. a composition) and have been regrouped into 3 distinguishable groups of inventions.

It should be noted that the group of inventions number 3 has been drafted as separate independent claims (claims 1,56,85,104 and 110) and therefore lacks conciseness.

The applicant if respectfully requested to reduce the number of independent claims in order to comply with the requirements of Art.6 PCT and Rule 13.1 PCT.

5b) Obscure functional definitions

It should be noted that the term "hostile biophysical environment" lacks clarity (Art. 6 PCT) and is interpreted in a broad sense (i.e. any compound that has an effect on the biophysical environment; this can include any compounds and in particular penetrating agents- see for example D4 p.17-27, p.9 L.23-25, claim 16).

Further the functional definition "stabilization polymer" in claim 111 has a very **broad and vague** scope rendering the limit of protection unclear.

The only "stabilizing polymer" described and exemplified in the present application is xanthan gum, which may be considered as a gelling agent, a thickening agent, or whatever...

Unless the applicant shows the contrary, it would be assumed that the polymers used in the compositions of D1 or D2 function also as stabilizing polymers (see in particular D1 §189-195).

It should be reminded that an unclear term cannot be allowed in a claim if the term is essential having regard to the invention.

5c) Result to be achieved

The definitions in claims 3-5, 16 and 29 such as "wherein the composition is stable when [...]", "wherein the hostile biophysical environment is capable of driving the ibuprofen [...] through stratum corneum", "wherein the hostile biophysical environment is able to cause the nitric oxide donor to migrate from [...]" do not delimit the scope of the protection to be sought and are rather to be construed as an attempt to define the invention by a **result to be achieved**, in particular when they only amount to claiming the underlying technical problem.

Such definitions are **not allowable** because it appears possible to define the subject-matter in more concrete terms, viz. in terms of how the effect is to be achieved by incorporating for example the type and amount of excipients used,...

Hence applicant's attention is drawn with the fact such definitions in the said claims **are not recognized as a technical feature** that can confer novelty to the application, **but as a result to be achieved and therefore would be ignored when assessing novelty**.

5d) Exotic parameter

Claim 28 contains an exotic parameter "a component having an octanol-water partition coefficient of at least 1000" which is unclear and unallowable according to Art.6 PCT.

5e) The term "consisting **essentially** of" in claim 85 has no limiting meaning. It would be interpreted as meaning "comprising", NOT "consisting of".

6) The attention of the applicant is drawn to the fact that the application may not be amended in such a way that it contains subject-matter which extends beyond the content of the application as filed.

In order to facilitate the examination of the conformity of the amended application with the requirements of Article 34(2)(b) PCT, the applicant is requested to clearly identify the amendments carried out, no matter whether they concern amendments by addition, replacement or deletion, and to indicate the passages of the application as filed

on which these amendments are based (see also Rule 66.8(a) PCT). Preferably these indications should be submitted in handwritten form on a copy of the relevant parts of the application as filed.

7) The applicant is kindly requested to take account of the above objections and give convincing argumentations. It is not at present apparent which part of the application could serve as a basis for a new, allowable claim. Should the applicant nevertheless regard some particular matter as patentable, an independent claim should be filed taking account of Rule 6.3(b) (i), (ii) PCT (two part form claim). The applicant should also indicate in the letter of reply the difference of the subject-matter of the new claim vis-à-vis the state of the art and the significance thereof.

Possible steps after receipt of the international search report (ISR) and written opinion of the International Searching Authority (WO-ISA)

General information	For all international applications filed on or after 01/01/2004 the competent ISA will establish an ISR. It is accompanied by the WO-ISA. Unlike the former written opinion of the IPEA (Rule 66.2 PCT), the WO-ISA is not meant to be responded to, but to be taken into consideration for further procedural steps. This document explains about the possibilities.
Amending claims under Art. 19 PCT	Within 2 months after the date of mailing of the ISR and the WO-ISA the applicant may file amended claims under Art. 19 PCT directly with the International Bureau of WIPO. The PCT reform of 2004 did not change this procedure. For further information please see Rule 46 PCT as well as form PCT/ISA/220 and the corresponding Notes to form PCT/ISA/220.
Filing a demand for international preliminary examination	<p>In principle, the WO-ISA will be considered as the written opinion of the IPEA. This should, in many cases, make it unnecessary to file a demand for international preliminary examination. If the applicant nevertheless wishes to file a demand this must be done before expiry of 3 months after the date of mailing of the ISR/ WO-ISA or 22 months after priority date, whichever expires later (Rule 54bis PCT). Amendments under Art. 34 PCT can be filed with the IPEA as before, normally at the same time as filing the demand (Rule 66.1 (b) PCT).</p> <p>If a demand for international preliminary examination is filed and no comments/amendments have been received the WO-ISA will be transformed by the IPEA into an IPRP (International Preliminary Report on Patentability) which would merely reflect the content of the WO-ISA. The demand can still be withdrawn (Art. 37 PCT).</p>
Filing informal comments	After receipt of the ISR/WO-ISA the applicant may file informal comments on the WO-ISA directly with the International Bureau of WIPO. These will be communicated to the designated Offices together with the IPRP (International Preliminary Report on Patentability) at 30 months from the priority date. Please also refer to the next box.
End of the international phase	At the end of the international phase the International Bureau of WIPO will transform the WO-ISA or, if a demand was filed, the written opinion of the IPEA into the IPRP, which will then be transmitted together with possible informal comments to the designated Offices. The IPRP replaces the former IPER (international preliminary examination report).
Relevant PCT Rules and more information	Rule 43 PCT, Rule 43bis PCT, Rule 44 PCT, Rule 44bis PCT, PCT Newsletter 12/2003, OJ 11/2003, OJ 12/2003